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Surgical Management of the Adrenal Glands in the Multiple Endocrine Neoplasia Type II Syndrome

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During a 30-year period (1951–1981), seventeen patients underwent bilateral adrenalectomy for established adrenal medullary disease with catecholamine excess. Fourteen patients had the MEN IIa syndrome and 3 had the MEN IIb syndrome. There was no major operative morbidity and no operative mortality.

One patient died 23 months after initial operation because of metastatic pheochromocytoma. The remaining patients were followed for a mean of 129 months and all were personally interviewed. Three patients had 7 uneventful pregnancies. Twelve patients underwent 23 other surgical procedures requiring general anesthesia during the follow-up period without any morbidity. Two patients have metastatic pheochromocytoma; 3 have clinical metastatic medullary thyroid carcinoma; 5 patients have high calcitonin values and 6 patients are in excellent health at intervals of 15, 27, 58, 110, 134, and 373 months following resection. The need for adrenal replacement therapy has not caused significant problems in any patient.

The results of this study confirm that bilateral total adrenalectomy is a safe modality for the treatment of adrenal medullary disease in this syndrome and that it does not produce significant long-term morbidity.

In 1968, it was apparent to Steiner et al. [1] that there were two distinct familial multiple endocrine neoplasia syndromes—the first described by Wermer [2], characterized by pituitary, parathyroid, and pancreatic islet involvement, and the second, reported by Sipple [3], which today is characterized by medullary carcinoma of the thyroid gland (MTC), pheochromocytoma, and parathyroid hyperplasia. In order to emphasize that these 2 associations were genetically distinct (there had been some speculation that they might be related because of the occurrence of parathyroid disease in both), Steiner et al. suggested that the Wermer and Sipple tumor combinations be designated multiple endocrine neoplasia, type I (MEN I) and multiple endocrine neoplasia, type II (MEN II), respectively.

The majority of patients with MEN II have a normal appearance but a minority have an unusual phenotypic appearance due to a diffuse ganglioneuromatosis which causes enlargement of the lips, nodules on the anterior one-third of the tongue and eyelids, and a marfanoid habitus. To recognize the similarity of the endocrine tumors in the two groups, but contrast their biological behavior and phenotype, our group [4] suggested the designations MEN IIa and IIb for them, the latter referring to patients with the unusual appearance. An additional familial multiple endocrine neoplasia syndrome has recently been described—the association of pheochromocytoma and islet cell tumor of the pancreas [5].

In patients with MEN IIa and IIb, the adrenal medullary pathology is uniformly bilateral and multicentric. Adrenal medullary hyperplasia (diffuse or nodular) is presumably the pathologic precursor of pheochromocytoma [6]. The pathologic spectrum in these syndromes ranges from diffuse medullary hyperplasia through diffuse and nodular medullary hyperplasia to typical pheochromocytomas, bilateral and multicentric [7].

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The surgical management of the adrenal medullary disease in this syndrome remains controversial. Our group [7–9] has recommended bilateral total adrenalectomy once a diagnosis has been clearly established. Others have not agreed and recommend that a decision for contralateral adrenalectomy be based on the size of the ipsilateral tumor and clear demonstration of catecholamine excess. The major argument against bilateral total adrenalectomy has been fear of increased morbidity and mortality caused by absence of the adrenal glands.

We have reviewed our experience with 17 patients having MEN II who had adrenal surgery to determine whether our recommendation regarding bilateral total adrenalectomy requires change.

Methods

Between 1951 and 1982, 17 patients with MEN II underwent bilateral adrenalectomy. Their medical records were abstracted and additional follow-up obtained in all living patients (16/17) by personal interview. The mean duration from operation to follow-up was 123 months (range 15 to 375 months).

Results

Diagnosis and Operation. Seventeen patients underwent bilateral adrenalectomy at the Mayo Clinic; 10 were female with a mean age of 26 years (range 12–47 years) and 7 were male with a mean age of 42 years (range 26–61 years). Fourteen patients had MEN IIa and 3 had MEN IIb. MTC or its precursor, C-cell hyperplasia, was present in 17. Nine of those with MEN IIa had co-existent parathyroid disease. A family history of MEN II was positive in 13 patients [10]; 4 are presumed to represent initial mutation. All patients had unequivocally increased urinary contents of fractionated or total catecholamines and/or their metabolites, metanephrine and vanillylmandelic acid. Tests for catecholamine excess were initiated for 3 reasons: symptoms of pheochromocytoma (5 patients), presence of MTC (6), and part of the routine screening of kindreds (6).

After appropriate glucocorticoid preparation and adrenergic blockade (when it became available), 14 patients underwent bilateral total adrenalectomy. Two were treated in the early 1950's by enucleation and the third, recently, by similar enucleation in a concerted effort to conserve adrenal cortical function. The latter patient is a commercial airline pilot who refused bilateral total adrenalectomy since he would have lost his livelihood if an anadrenal state was surgically created. Although he is back flying and requires no adrenal corticoid replacement ± 18 months following operation, we are somewhat uneasy about his long-term course in view of the "less than standard" surgical procedure performed. In the entire group, there was no major operative morbidity or mortality.

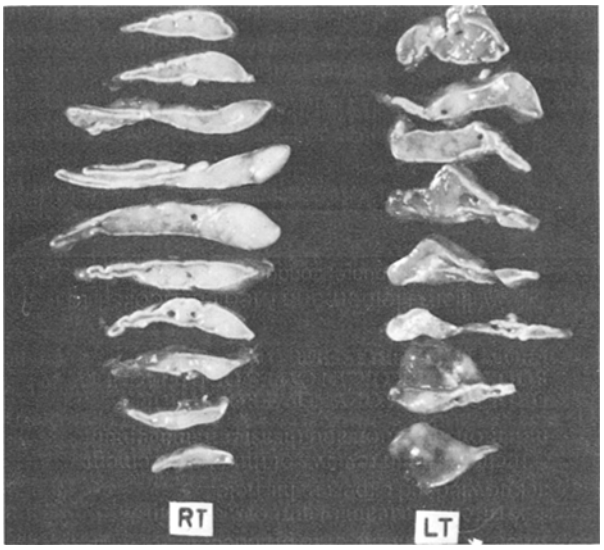

Fig. 1. Pheochromocytoma with bilateral diffuse and nodular medullary hyperplasia. The right gland contains a diffusely expanded medulla. Pheochromocytoma is present in the left gland which also shows diffuse medullary thickening.

Pathological Findings

Gross. All patients had bilateral adrenal medullary disease. The glands ranged in size from normal to 13 × 9 × 7 cm, and in weight from 3.4 to 480 g. The medulla was expanded in all cases as a result of either nodule formation (2 mm to 6 × 5 × 5 cm in diameter) or diffuse thickening or both (Fig. 1). The expansion was classified as follows: nodules measuring more than 1 cm in diameter were designated "pheochromocytoma," nodules measuring less than 1 cm in diameter were titled "nodular medullary hyperplasia," and the term "diffuse medullary hyperplasia" was applied to those cases in which diffuse enlargement of the medulla was evident. The findings are summarized in Table 1. Two or more tumor nodules (maximum 6) were present in 18 glands (Fig. 2) and a single nodule was present in 6 glands. As a result of the amount of configuration of the medullary enlargement, the glands varied in shape from normal to spherical to complexly lobulated. When more than one tumor nodule was present, the nodules usually differed in color, ranging from purplish-pink to red to tan to white. Involvement of the glands was relatively symmetric in 12 patients and markedly asymmetric

Table 1. Pathological findings in 17 patients with MEN type II.

Bilateral pheochromocytoma (P)	11[a]
Unilateral P + contralateral adrenal medullary hyperplasia (AMH)	5
Bilateral AMH only	1

[a]Two patients had AMH as well.

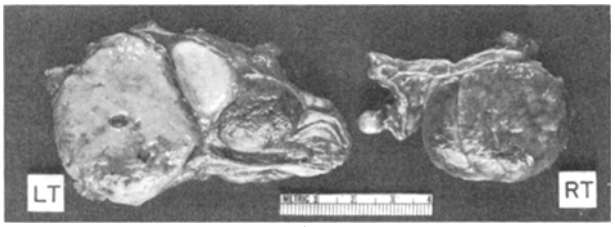

Fig. 2. Bilateral multicentric pheochromocytomas. The right gland contains 2 tumors, one spherical, the other semilunar. Three tumors of different color are present in the left gland.

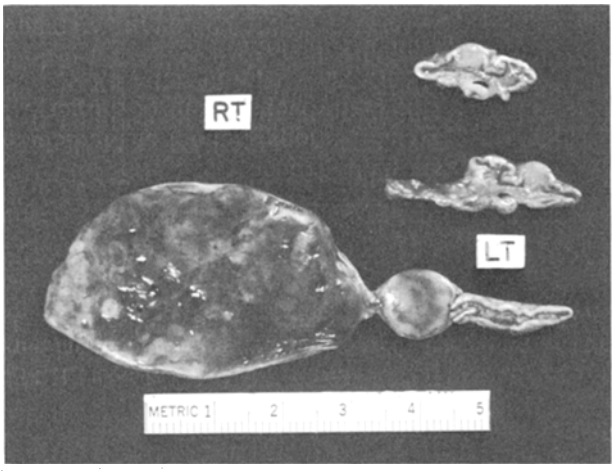

Fig. 3. Unilateral multicentric pheochromocytoma and contralateral nodular medullary hyperplasia. Asymmetry between the glands is readily apparent; the right and left glands weighed 80 and 2.4 g, respectively. Two pheochromocytomas are present in the right gland. The left gland exhibits nodular medullary hyperplasia.

in 5. Among the latter, the smaller gland was normal in shape and about normal in weight; in the most extreme case, the weights of the adrenal glands were 80 and 3.4 g, respectively (Fig. 3). Bilateral diffuse cortical hyperplasia associated with an ACTH-secreting medullary thyroid carcinoma was additionally present in 1 patient (Fig. 4).

Microscopic. Marked variability of several features was the striking finding. The tumors varied in cellular arrangement (small or large cell clusters, or sheets of cells) (Fig. 5), staining of the cell cytoplasm (basophilic or amphophilic or eosinophilic or brown), cell size (small to large), and cell shape

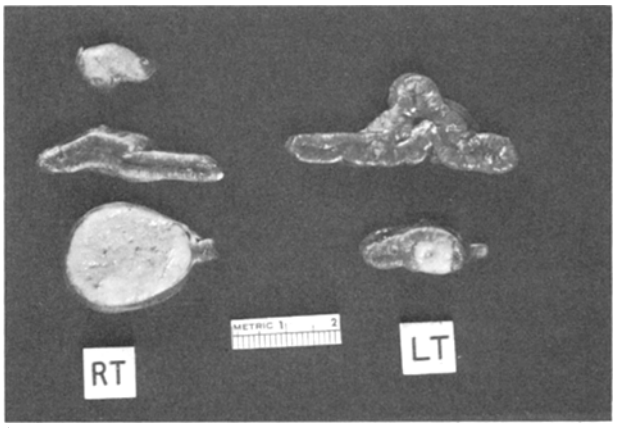

Fig. 4. Bilateral medullary and cortical disease. The right and left medullae are expanded by pheochromocytoma and nodular medullary hyperplasia, respectively. The cortex, which is dark brown in color, is thickened bilaterally.

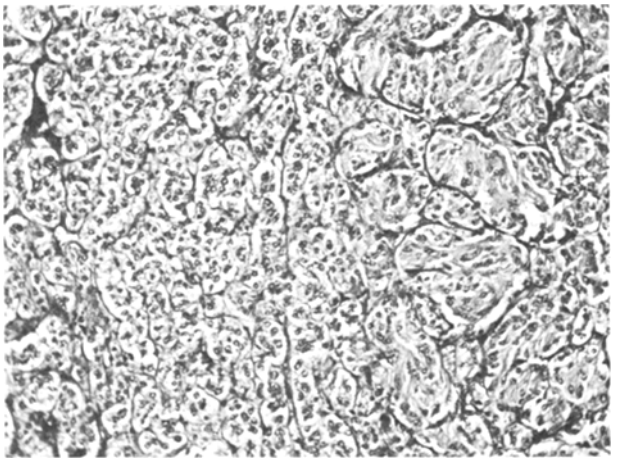

Fig. 5. Pheochromocytoma. Typical juxtaposition of histologically different tumor patterns. Relatively small cells cluster to form small clusters *(left)* and larger cells are aggregated into larger cell nests *(right)*. H & E × 160.

(polygonal to slightly spindle). Nodularity not detectable on gross examination was commonly observed in diffusely thickened medulla (Fig. 6).

Patient Status

Follow-up information is outlined in Table 2. One patient died 23 months postoperatively of recurrent pheochromocytomas. Sixteen patients are alive at a mean of 129 months (range 15–375 months) following operation. Recurrence of pheochromocytoma was present in 3 patients at 23 months (dead) and 360 and 375 months (alive) postoperatively. In 2 of these, the initial operation was subtotal adrenalectomy. The remaining 14 patients have no evidence of pheochromocytoma. Three of

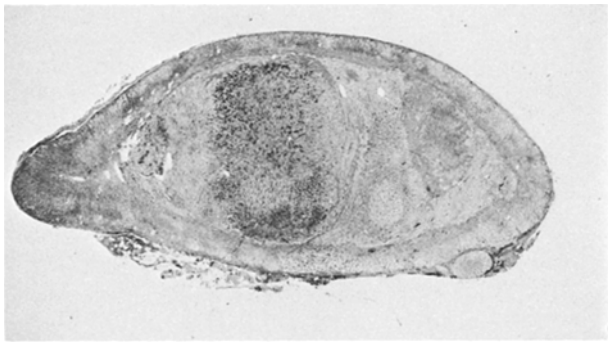

Fig. 6. Diffuse and nodular medullary hyperplasia. Microscopic examination of what appeared to be grossly thickened medulla shows 3 nodules (nodular medullary hyperplasia) set in a background of diffusely thickened medulla (diffuse medullary hyperplasia). H & E × 8.

Table 2. Results in 17 patients with MEN type II.

Status[a]	Number	Time postoperatively (months)
Died (recurrent P)	1	23
Alive with recurrent P	2	375, 360
Alive with MTC mets	3	110, 43, 26
Alive with elevated iCT	5	130, 100, 86, 78, 36
Alive with normal iCT	6	373, 134, 110, 58, 27, 15

[a]P = pheochromocytoma; MTC = medullary thyroid carcinoma; iCT = immunoreactive thyrocalcitonin.

these have metastatic MTC. Five have high concentrations of plasma immunoreactive calcitonin (iCT). Six have normal iCT concentrations.

Problems Caused by Adrenal Absence

A major reservation concerning our recommendation of bilateral total adrenalectomy for adrenal medullary disease in MEN II has been the possibility of increased morbidity in patients without adrenal glands. Because of this reservation, each patient was questioned thoroughly about adrenal replacement medications and for the problems outlined in Table 3. Without exception, all patients had had instructions in the use of gluco-and mineralocorticoids, understood the need to triple their glucocorticoid dose at times of physiologic stress, knew that prior to additional surgical procedures parenteral glucocorticoid therapy was necessary, and had been advised to wear an external identification such as Medic-Alert®.

Two of 3 patients who had subtotal adrenalectomy do not require adrenal steroid replacement. In the 15 supplemented patients, maintenance glucocorticoid replacement doses were as follows: prednisone, 5.0 mg A.M. and 2.5 mg P.M. (4 patients); hydrocortisone, 20 mg A.M. and 10 mg P.M. (4); cortisone acetate, 10 mg 3 times a day (3); cortisone acetate, 50 mg 4 times a day in divided doses (2); and cortisone acetate, 25 mg 4 times a day (2). Eleven patients require mineralocorticoid replacement with fludrocortisone acetate; their doses were 0.05 mg 4 times a day (2), 0.1 mg 4 times a day (7), and 0.2 mg 4 times a day (2).

Table 3 collates the results of direct questioning about possible problems that had occurred as the result of total adrenalectomy. One patient with MEN IIb, metastatic MTC, and severe diarrhea had developed orthostatic lightheadedness after self-reduction of fludrocortisone acetate. Eight patients (53%) had not obtained or did not routinely wear a crisis identification emblem. Twenty-three surgical procedures had occurred following adrenalectomy in the 15 patients (Table 4). In each case, appropriate increased glucocorticoid medication had been given and no patient developed symptoms of adrenal insufficiency. Eight pregnancies occurred in 3 of the patients; 7 went to term without complication; there was 1 miscarriage. Five patients had tripled their oral glucocorticoid replacement during stress: viral infections (3 patients), an episode of MTC-associated diarrhea (1), and during a brief period of vitamin D-induced hypercalcemia (1). It is readily apparent that few patients had significant problems as a result of bilateral total adrenalectomy.

Discussion

Because the MEN II syndrome is rare, no single center has had sufficient experience with the adrenal medullary component of the disease to establish clearly the best surgical treatment for it. Some have advocated initial unilateral adrenalectomy, while Tibblin et al. [11] have suggested that primary contralateral adrenalectomy is only indicated if the pheochromocytoma on the initial side is 5 cm or larger. Our past management has been to perform bilateral total adrenalectomy in affected patients, once excess catecholamine secretion was demonstrated. We undertook this review of our personal management and that of other centers to establish a framework for management in the next decade.

Analysis of the outcome of surgery in our patients shows that the operative morbidity was negligible and there was no operative mortality. Creation of an Addisonian state has not constituted an undue hazard for our patients. The information we obtained from detailed questions of them substantiated our clinical impression that replacement therapy with usual amounts of prednisone and fludrocortisone acetate is comfortably tolerable, and they had not had complications associated with

Table 3. Problems associated with absence of adrenal glands.

Problem	Patients exposed or questioned	Patients with problem	% Patients with problem
Cardiovascular			
Orthostasis, hypotension, shock	15	1	7
Crisis identification			
Failure to wear Medic-Alert® or similar identification	15	8	53
Emergency treatment			
Had to use intravenous or intramuscular glucosteroids and/or 0.9% NaCl	15	0	0
Gastrointestinal			
Unexplained anorexia, nausea, vomiting, abdominal pain, weight loss	15	0	0
Mental			
Lethargy, apathy, confusion, psychosis	15	0	0
Metabolism			
Hypoglycemia, hypercalcemia, decreased growth	15	0	0
Operations			
Difficulties with operations	15 (23 operations)	0	0
Pituitary			
Increased mucocutaneous pigmentation	15	0	0
Pregnancy complications			
Miscarriage, premature labor, hypotension, shock	3 (7 term pregnancies)	1	33
Renal			
Weakness, salt craving, hyperkalemia	15	0	0
Stress			
Impaired tolerance to trauma, infection, fasting	15 (5 patients treated)	0	0

Table 4. Post-adrenalectomy surgical procedures/pregnancies.

	Number	Patients	Complications
Pregnancies	8	3	1 (miscarriage)
Operations (requiring general anesthesia)	23	12	0

total adrenalectomy. In fact, with follow-up averaging 11 years and as long as 30 years, no patient in this series has experienced a significant increase of problems related to absent adrenals—this despite the need for subsequent operations and the occurrence of pregnancy (Table 3).

When is adrenalectomy indicated for MEN II? We think the most logical indication is a clearly demonstrable hypersecretion of catecholamines and/or their metabolites. All of our patients met this criterion, and all had bilateral adrenal medullary disease. Harrison and Gann [12] have urged this criterion in a recent editorial. In patients from affected kindreds, but without hypersecretion of catecholamines, lesser indications for exploration would appear to be an adrenal mass of a certain size (greater than 3 cm) or a well-documented sequential increase in adrenal size. However, we believe that once the diagnosis has been made, there is no role for long-term medical observation unless the patient has distinct contraindications to operation. The danger of fatal hypertensive crisis during other surgical procedures is very real. One patient, who had thyroidectomy for MTC at our institution, died during Caesarean section elsewhere with uncontrolled hypertension; at autopsy, bilateral pheochromocytomas were found. Our experience does not allow us to address what should be done for MEN II patients who are normotensive with normal catecholamine studies, but who have positive ^{131}I metaiodobenzylguanidine scans [13].

Once an indication for surgery has been established, what is the operation of choice for adrenal medullary disease in MEN II? Should surgeons remove only enlarged adrenal glands containing pheochromocytomas, or should bilateral total adrenalectomy be the initial surgical procedure of choice? Because we are still learning about the natural history of this component of the MEN II syndrome and because it shows some variation in different families, it is difficult to give an absolute answer to this question. Several facts are known. First, in our patients, the grossly uninvolved adrenal gland was always pathologically abnormal, a finding consistent with Knudson's [10–12] two-mutational event theory of the initiation of neoplasia. Second, present radiological techniques and even direct operative visualization and palpation cannot uniformly be relied on for accurate diagnosis of adrenal medullary disease. Third, a review of clinical results in 72 patients published from 1975 [7, 16–21] indi-

cates that the majority—63 (88%)—required total adrenalectomy. Of the 20 who had initial unilateral adrenalectomy, 11 (55%) required completion or total adrenalectomy within a mean of 4.8 years (range, X months–16 years). Finally, one of our initial patients treated by enucleation developed metastatic pheochromocytoma which required reoperation; she is alive and functions well by using alpha- and beta-adrenergic blocking agents. These facts suggest the advisability of an initial total adrenalectomy, unless outweighed by other considerations.

The virulence of the adrenal medullary component of the syndrome, in particular families, is a consideration that should be taken into account when deciding on treatment. In some families, pheochromocytoma is the dominant manifestation of the syndrome [22]. The tumors manifest at a relatively young age, before the MTC, and they are large and hormonally active. This type of presentation occurred in 3 siblings under the age of 25 years and there were subsequent metastases in one. We think such circumstances should encourage us to treat adrenal medullary disease in other affected members of this family aggressively. Indeed, it prompted us to perform bilateral total adrenalectomy in the daughter of 1 of the 3 who, at age 12 years, had a slight elevation of the urinary content of VMA. Bilateral diffuse adrenal medullary hyperplasia was present.

Another consideration is the size of the individual adrenal gland in relation to patient age. Finding gross disease in one gland and no abnormality on palpation in the other, we would be more inclined to perform bilateral adrenalectomy in a younger rather than in an older patient. The former has more years to develop contralateral disease. In this regard, we cite the findings in 2 patients, ages 14 and 27 years. Both had similar findings in the adrenals; gross involvement on one side and no palpable abnormality on the other. The younger patient was a member of a kindred in which pheochromocytoma had been functional in other members. The older patient was a member of a family in which MTC was the dominant manifestation of MEN II, and pheochromocytoma was uncommon. Both were treated by bilateral adrenalectomy. Pathologic examination showed diffuse and nodular hyperplasia (younger patient) and nodular hyperplasia only (older patient), respectively, in the small glands of each patient. Total adrenalectomy seems eminently justifiable in the former patient because of her age and the prevalence of functioning pheochromocytoma in other members of her family. Total adrenalectomy was also justified in the older patient because nodular medullary hyperplasia was found in the clinically normal gland (Fig. 3). We do, however, recognize that an argument could be made for not removing the palpably normal gland because of the patient's age and the low clinical expressivity of pheochromocytoma in her family.

This study tends to confirm our surgical philosophy regarding initial total adrenalectomy in patients with the MEN II syndrome. The extremely low operative morbidity and mortality rates coupled with excellent long-term results would seem to outweigh the potentially lethal hemodynamic and malignant complications that may arise from remaining adrenal medullary tissue. However, there may be rare exceptions to this philosophy in individual patients when certain characteristics and manifestations of this fascinating syndrome are taken into consideration.

Résumé

Pendant une période de 30 ans, de 1951 à 1981, 17 sujets ont subi une adrénalectomie bilatérale par une affection de la médullo-surrénale s'accompagnant d'un taux anormalement élevé de catécholamines. Quatorze d'entre eux présentaient un syndrôme MEN IIa et trois un syndrome MEN IIb. La double adrénalectomie entraîna ni complication, ni décès.

Un malade mourut 23 mois après l'intervention de métastases alors qu'il avait été opéré pour phéochromocytome. Les 16 autres sujets furent suivis pendant 129 mois en moyenne. Trois des opérées présentèrent sept grossesses normales. Douze subirent 23 interventions chirurgicales diverses conduites sous anesthésie générale sans être victimes de complications. Deux opérés présentent des phéochromocytomes métastatiques, trois des cancers thyroïdiens médullaires métastatiques, cinq malades accusent un taux élevé de calcitonine et six sont en excellente santé, respectivement 15, 17, 58, 110, 134 et 373 mois après la double adrénalectomie. L'hormonothérapie supplétive n'a entraîné aucun trouble chez les opérés.

Les résultats de cette étude montrent que l'adrénalectomie bilatérale est le traitement efficace de ce type d'affection et qu'elle n'entraîne aucune morbidité à long terme.

Resumen

En pacientes con síndrome de neoplasia endocrina múltiple tipos IIa y IIb (MEN IIa y MEN IIb), la patología adrenal medular uniformemente es bilateral y multicéntrica. La hiperplasia adrenal medular (difusa o nodular) es presumiblemente la entidad patológica precursora del feocromocitoma. El

espectro anatomo-patológico en estos dos tipos del síndrome varía desde la hiperplasia medular difusa y nodular hasta el feocromocitoma típico, bilateral y multicéntrico. El tratamiento quirúrgico de la enfermedad adrenal medular en este síndrome es todavía motivo de controversia. Nuestro grupo ha recomendado adrenalectomía bilateral total una vez que el diagnóstico haya sido establecido.

En el curso de un período de 30 años (1951–1981), 17 pacientes fueron sometidos a adrenalectomía bilateral por enfermedad adrenal medular con exceso de catecolamina. Catorce pacientes presentaban síndrome MEN IIa y tres MEN IIb. No hubo morbilidad operatoria mayor ni mortalidad operatoria.

Un paciente murió 23 meses después de la operación inicial debido a feocromocitoma metastásico. El resto de los pacientes fueron seguidos por un promedio de 129 meses y todos fueron entrevistados personalmente. Tres pacientes tuvieron embarazos sin complicaciones. Doce pacientes fueron sometidos a otros procedimientos quirúrgicos que requirieron anestesia general en el curso del seguimiento postoperatorio, sin morbilidad alguna. Dos pacientes presentaron feocromocitoma metastásico; tres presentaron carcinoma medular tiroideo metastásico; cinco exhibieron valores altos de calcitonina y seis pacientes se encuentran en excelente estado de salud a intervalos de 15, 27, 58, 110, 134 y 373 meses depués de la resección. La necesidad de terapia de reemplazo suprarrenal no ha causado problema de significación en paciente alguno.

Los resultados de este estudio confirman que la adrenalectomía bilateral total es una modalidad segura y eficaz para el tratamiento de la enfermedad adrenal medular en este síndrome, y que no resulta en morbilidad de significación a largo plazo.

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Invited Commentary

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The clinical identification of the MEN II syndrome and its subsequent association with abnormal release of calcitonin and catecholamines represent a major breakthrough in early tumor detection. The availability of sophisticated hormone assays has given us tumor markers of high specificity creating unique possibilities to detect and follow the development of these fascinating syndromes. Histomorphological studies indicate that in affected family members the C-cell mass as well as the adrenal medullary tissue is involved in a hyperplastic process usually of nodular type. The tumor formation then occurs multicentrically. With an increasing number of families reported, it is becoming obvious that there exists a considerable interfamilial variation in the expressivity of the disease. This is true for the time of onset, extent of involvement, tendency to malignancy, and virulence of the disease. The diagnostic tools used in these kindreds undergo a successive refinement, for example, improved provocation test, selective venous catheterisation for blood sampling, and isotopic studies with MIBG. This development leads to an earlier diagnosis, with frequent detection in the stage of asymptomatic hyperplasia. This has resulted in a certain insecurity as to the proper timing and extent of the surgical procedures to be applied. There is a general agreement that the C-cell tumors, due to their high degree of malignancy, should be treated by radical removal of the affected organ. In the adrenal medulla, malignant degeneration is rare.

The Mayo group is to be complimented for their important and interesting report. The consequent treatment and thorough follow-up of the patients over a long period of time give their experiences a particular weight. In a similar study we recently presented our material consisting of 18 patients treated and followed during a 15-year period [1]. In contrast to the Mayo material our report dealt exclusively with the MEN IIa syndrome, a fact that might be of importance since the b variant is considered to have a more malignant course both as to the involvement of the C cells and the adrenal medulla.

In many respects, similar observations were made in the 2 reports. The medullary carcinoma of the thyroid was more common than the pheochromocytoma. Both seemed to develop from hyperplasia usually of nodular type. There was a general involvement of the affected organ. The disease had a varying expressivity from family to family. Most patients were recruited as a result of an MCT diagnosis or by family screening. The absence of more detailed clinical data in the Mayo report makes a comparison in this respect impossible.

In our material 6 patients were clinically asymptomatic except for biochemical findings. Only half of them had hypertension. Hyperparathyroidism occurred frequently in the Mayo material while it was absent in our patients. Three patients of the Mayo material had metastatic pheochromocytoma while malignancy was completely absent in our material. In the 10 independent MEN IIa families that hitherto have been found in Sweden, no case of malignant pheochromocytoma has been described. This might be of some interest since several of the families described from various centers in the United States are descendants of our original family described by Ljunberg [2].

Based on their observations and experience, the Mayo group advocates initial bilateral adrenalectomy as the most preferred treatment in MEN II syndromes. The main reasons for this opinion are the risk of malignancy and the dangers related to an undiagnosed pheochromocytoma. In our experience malignant pheochromocytoma is a rare event in the MEN IIa syndrome. It is not clear from the Mayo report whether the malignant cases had a MEN IIa or IIb syndrome. We agree that both adrenals should be removed in a pheochromocytoma patient belonging to a family with malignant adrenal medullary manifestations. We also agree that macroscopically involved adrenals have to be removed. However, we disagree with the prophylactic removal of a macroscopically normal adrenal in a patient undergoing adrenalectomy for a pheochromocytoma on the other side, particularly if the largest tumor has a diameter of less than 5 cm, reflecting a relatively minor degree of progression. The reason for this opinion is not the surgical risk